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United States Patent [19]**Carlino et al.**[11] **Patent Number:** **5,527,776**[45] **Date of Patent:** **Jun. 18, 1996**[54] **TREATMENT OF IMMUNOLOGIC AND HEMATOLOGIC DISORDERS WITH IGFBP ALONE OR COMPLEXED WITH IGF**[75] Inventors: **Joseph A. Carlino**, San Leandro;
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of Calif.[73] Assignee: **Celtrix Pharmaceuticals**[21] Appl. No.: **393,249**[22] Filed: **Feb. 23, 1995****Related U.S. Application Data**

[63] Continuation of Ser. No. 124,410, Sep. 20, 1993, abandoned.

[51] **Int. Cl.⁶** **C07K 2/00**; C07K 14/00;
A61K 38/27[52] **U.S. Cl.** **514/12**; 530/324; 530/350;
530/399[58] **Field of Search** 530/324, 350,
530/399; 514/12[56] **References Cited****U.S. PATENT DOCUMENTS**4,876,242 10/1989 Applebaum et al. 514/3
5,187,151 2/1993 Clark et al. 514/3
5,202,119 4/1993 Clark et al. 424/88**FOREIGN PATENT DOCUMENTS**W089/05822 6/1989 Australia .
0128733 12/1984 European Pat. Off. .
W092/13556 8/1992 WIPO .
W093/00110 1/1993 WIPO .**OTHER PUBLICATIONS**Blum et al., "Plasma IGFBP-3 levels as clinical indicators" *Modern Concepts in Insulin-like Growth Factors* (1991) Spencer, E. M., ed., Elsevier Publishers, New York pp. 381-393.Rinderknecht et al., "Polypeptides with nonsuppressible insulin-like and cell-growth promoting activities in human serum: Isolation, chemical characterization, and some biological properties of forms I and II" *Proc. Natl. Acad. Sci. USA* (1976) 73:2365-2369.Baxter et al., "Growth hormone-dependent insulin-like growth factor (IGF) binding protein from human plasma differs from other human IGF binding proteins" *Biochem. Biophys. Res. Commun.* (1986) 139:1256-1261.Sommer et al., "Molecular genetics and actions of recombinant insulin-like growth factor binding protein-3" *Modern Concepts in Insulin-like Growth Factors* (1991) Spencer, E. M., ed., Elsevier Publishers, New York, pp. 715-728.Skottner et al., "Anabolic and tissue repair functions of recombinant insulin-like growth factor I" *Acta Paediatr. Scand.* (1990) 367:63-66.Gala, "Prolactin and growth hormone in the regulation of the immune system" *PSEBM* (1991) 198:513-527.Murphy et al., "Immunologic and hematologic effects of neuroendocrine hormones" *J. Immunol.* (1992) 148:3799-3805.Binz et al., "Repopulation of the atrophied thymus in diabetic rats by insulin-like growth factor I" *Proc. Natl. Acad. Sci. USA* (1990) 87:3690-3694.Hodgkinson et al., "Distribution of circulating insulin-like growth factor I (IGF-I)" into tissues *Endocrinology* (1991) 129(4):2085-2093.Beschocmer et al., "Enhancement of thymic recovery after cyclosporine by recombinant human growth hormone and insulin-like growth factor I" *Transplantation* (1991) 52(2):879-884.Aron et al., "Insulin-like growth factor I and erythropoiesis" *BioFactors* (1992) 3(4):211-216.Quaife et al., "Histopathology associated with elevated levels of growth hormone and insulin-like growth factor I in transgenic mice" *Endocrinology* (1989) 124(1):40-48.Intebi et al., "Active B-Cell differentiation under PWM induction acromegaly" *Prog. Neuroendocrinol.* (1992) 5(1):62-69.Jennische et al., "Dynamic changes in insulin-like growth factor I immunoreactivity correlate to repair events in rat ear after freeze-thaw injury" *Exp. Mol. Pathol.* (1987) 47:193-201.Spencer et al., "Somatomedins: Do they play a pivotal role in wound healing?" *Growth Factors and Other Aspects of Wound Healing: Biological and Clinical Implications* (1988) Alan R. Liss Publishers, pp. 103-116.Baxter et al., "Characterization of immunoreactive insulin-like growth factor-I from leukocytes and its regulation by growth hormone" *Endocrinol.* (1991) 129(4):1727-1734.Stuart et al., "Insulin-like growth factor-I binds selectively to human peripheral blood monocytes and B-lymphocytes" *J. Clin. Endocrinol. Metab.* (1991) 72(5):1117-1122.Kooijman et al., "Expression of type I insulin-like growth factor receptors on human peripheral blood mononuclear cells" *Endocrinol.* (1992) 131:2244-2250.Marchav et al., "Enhancement of human granulopoiesis in vitro by biosynthetic insulin-like growth factor I/somatomedin C and human growth hormone" *J. Clin. Invest.* (1988) 81:791-797.

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ABSTRACT

This invention includes a method of treating subjects with immunologic and hematologic disorders, such as immune deficiencies and anemias characterized by deficient total hemoglobin. The treatment includes administering to the subject insulin-like growth factor binding protein-3 (IGFBP-3), alone or in a complex including an insulin-like growth factor (IGF), in an amount sufficient to improve the immunologic and/or hematologic disorder, for example, increasing the level of total hemoglobin or improving immune deficiencies, such as occur post-chemotherapy. Another aspect of the invention includes administering IGFBP-3 alone to treat IGF-driven lymphoproliferative conditions, such as leukemias, inflammatory skin diseases, and nasal polyps.

1 Claim, 3 Drawing Sheets